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RAB3 (7509C)
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12/6/99

DATA EVALUATION RECORD

STUDY TYPE: Acute Neurotoxicity Screen in Rats

OPPTS Number: 870.6200 Guideline Number: [81-8]

DP BARCODE: D249626 SUBMISSION CODE: S526363

P.C. CODE: 129122 TOX. CHEM. NO.: N/A

TEST MATERIAL (PURITY): N-(2,6-dichlorophenyl)-5-ethoxy-7-fluoro-[1,2,4]triazolo [1,5-C] pyrimidine-2-sulfonamide
(XDE-564, a.i 97.6%)

SYNONYMS: XDE-564, Diclosulam

CITATION: Mattsson, J., P. Spencer, and J. Quast. 1996. XDE-564: Acute Neurotoxicity Study in Fischer 344 Rats. The toxicology Research Laboratory, The Dow Chemical Company, Midland, MI. Laboratory report # DR-0313-5691-026. July, 1996. MRID # 44192601. Unpublished.

SPONSOR: Dow Elanco, Indianapolis, IN

EXECUTIVE SUMMARY:

In an acute neurotoxicity study (MRID # 44192601), rats (10/sex/group) received a single dose of XDE-564 (97.6% a.i.) by gavage (in methyl cellulose). Doses were 0, 200, 1000, or 2000 (a limit dose) mg/kg for both sexes. Clinical observations were recorded twice daily. Evaluation during the two-week study period included body weights, functional observational battery (FOB), motor activity and neuropathology. The FOB consisted of hand-held and open-field observations, grip performance, rectal temperature and landing foot splay testing. Animals were evaluated by FOB and motor activity assay once prior to exposure, on day 1 (beginning approximately 5 hours after dosing), and on days 8 and 15 of the study period. Body weights were determined on days -7,1,2,8 and 15 relative to the day of dosing (day 1). Cholinesterase inhibition was not evaluated.

At study termination on day 16, 5 rats/sex/group were perfused intracardially with glutaraldehyde/paraformaldhyde, and histopathological evaluation of peripheral and central nervous system tissue was performed on animals from the control and high dose groups only.

No evidence of neurotoxicological effects were observed at any of the dose levels. Furthermore,there were no compound-related effects in mortality, morbidity, clinical signs, body weight, FOB, motor activity or neuropathology.

Additionally, a gavage range-finding study (MRID # 44103522) was conducted to determine the benchmark dose (3 rats/sex). This dose-ranging study is acceptable.

A positive control data were submitted as three separate appendices, with different test chemicals, procedures, and dosage regiments. The opinion of the EPA reviewer is that the three studies were incompatable with the current study (MRID # 44192601). Consequently, the positive control data are rejected.

The LOAEL is not observed, based on lack of toxicity at any of the dose levels. The tentative NOAEL is 2000 mg/kg for both sexes, pending submission of requested information.

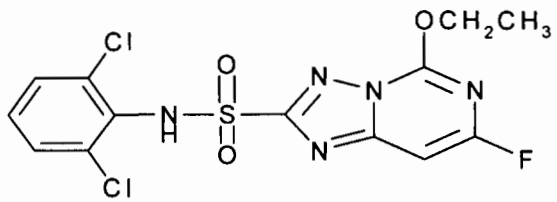
This acute neurotoxicity study is classified **Unacceptable/Guideline** pending submission of untransformed motor activity data and sufficient positive control data to satisfy EPA reviewers. This study does not satisfy the guideline requirement for an acute neurotoxicity study (81-8) in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: N-(2,6-dichlorophenyl)-5-ethoxy-7-fluoro-[1,2,4]triazolo [1,5-C] pyrimidine-2-sulfonamide, Diclosulam, XDE-564
   Stability of compound: Stable for 7 days in 0.5% aqueous methyl cellulose
   Lot/Batch #: DECO-151-86
   Purity: 97.6% ai
   Supplier: Dow Elanco, Indianapolis, IN
   Description: White powder
   CAS #: 145701-21-9
   Structure:



2. Vehicle and/or positive control:
   0.5% aqueous methyl cellulose, Lot/Batch #: Not provided

3. Test animals: Species: Rats
   Strain: Fischer 344
   Age and weight at study initiation: 8 weeks old
   Males: ≃ 210 g
   Females: ≃ 145 g
   Source: Charles River Laboratories, Kingston, New York
   Housing: Suspended stainless steel cages with wire-mesh floors, 2/cage during the acclimation period, and 1/cage during the study period.
   Diet: Certified Purina Chow # 5002 (Purina Mills Inc., St. Louis, MO), ad libitum
   Water: Municipal tap water, ad libitum
   Environmental conditions: Temperature: 21-23 °C
   Humidity: 40-60%
   Air changes: Not provided
   Photoperiod: 12-hour light-dark cycle
   Acclimation period: At least 1 week.

B. STUDY DESIGN:

1. In life dates - start: September 26, 1994
end: October 20, 1994

2. Animal assignment

Study Design: Animals were stratified by body weight, and randomly assigned, 10 animals/sex/group, to one of four treatment groups (Table 1). Animals were fasted overnight prior to dosing. Test material was mixed in 0.5% methyl cellulose, and administered by gavage as a single dose.
The test substance was administered in a staggered manner, 5 rats/sex/dose/day, over a four day period. The staggered administration of the test article was counterbalanced for dose groups. Individual doses were calculated based on animal weight.

TABLE 1: STUDY DESIGN FOR RATS ADMINISTERED XDE-564 BY ORAL GAVAGE[a].

Test Group	Dose to Animal *(mg/kg)*	Male	Female
Control	0	10	10
Low	200	10	10
Mid	1000	10	10
High	2000	10	10

a Data extracted from page 11, MRID # 44192601.

3. Dose-ranging study:
A gavage range-finding study (MRID # 44103522) was conducted to determine the benchmark dose (3 rats/sex). Based on a lack of clinical observations in a previous acute oral toxicity study in Fischer 344 rats, the benchmark dose study was conducted at 2000 mg/kg gavage dose (a limit dose). The rats in the benchmark dose study were observed about 30 min. post-dosing and hourly for the next 7 hours. No effects were noted at any time. Consequently, the dose levels for the acute neurotoxicity study reported herein were set at control, 200, 1000, and 2000 mg/kg.

4. Test material analysis
Test material was prepared by mixing the appropriate amount of the chemical (XDE-564) with 0.5% aqueous methyl cellulose. The identity of the test compound was confirmed by infrared spectoscopy (IR), mass spectrometry, and chromatographic retention. The purity of the compound was verified by HPLC, and was determined to

be 97.6%. The dosing solutions were analyzed for concentration prior to treatment, and the stability of the test article in methyl cellulose was based on previous toxicity studies.

5. Positive Controls: Positive control data were provided as three separate appendices within the major study:

Appendix C: Motor activity positive control
(Lab report ID # HET T1.05-018-002-REV), no date was given.
In this study, 5 groups of male Fischer rats (n=12/each) were given one single dose of either d-Amphetamine sulphate (i.p), 1 mg/kg, or 0.32 mg/kg, or 0.1 mg/kg. The other two groups received either saline solution, or no injections. Motor activity testing was then conducted in a similar manner to the current study. As expected, d-Amphetamine sulphate increased motor activity in a dose-dependent manner. Surprisingly, saline injection alone decreased motor activity, when compared to the non-injected controls.
After one week recovery period, the same rats were treated with chloropromazine (5 mg/kg, 2.24 mg/kg, and 0.5 mg/kg) in an inverted regimen. Rats that received the high and the middle dose of amphetamine, served as non-injected control and saline injected control for the chloropromazine study, respectively. Motor activity declined, as expected, and the effect of saline injection was also significant. The non-injected control and saline injected control for the amphetamine study served as the high and middle doses for chloropromazine, respectively. The low dose amphitamine group was injected with the low dose of chloropromazine in the second phase of the study (overlap group).
These data are considered inadequate and unacceptable by the EPA reviewer for the following reasons:
1. Using the same group of rats (recycling animals) to test motor activity after administration of
d-Amphitamine, then one week later injecting the same animals with chloropromazine, is unacceptable scientifically. Two groups of rats with proper controls should be utilized for such a study.
2. The test compound in the original study was administered by oral gavage, while in the motor activity portion of the positive control data, test compounds were administered by i.p. injections.
3. The significant response of rats to i.p. injections of saline is unusual and troublesome.
4. No date was given for study performance, therefore it is not clear whether it was performed within a reasonable time frame of the current study;
5. The number and length of epochs were different from those used for this study.
6. It is not clear whether the 100 msec cutoff for inclusion of a movement, used in the current study, was used for the positive control study.
7. Only male rats were used in the positive control study.

Appendix D: FOB proficiency report:
(Lab report ID # HET T1.05-022-001)
1. This appendix was originally provided to support another study entitled "Sulfuryl Fluoride: Elecrto-diagnostic, FOB and motor activity evaluation of nervous system effects from short-term exposure".
2. The above mentioned study was not executed at the same time as the current study (MRID # 44192601). The Sulfuryl Fluoride study was dated 07/27/93, while the current study was dated 07/09/1996. 3. The Sulfuryl Fluoride study was authored by R.R.Albee, P.J.Spencer and J.L.Mattson. Their individual roles and their specific training during the execution of that study is not known. It is not known whether these three individuals have participated in executing that study, or only authored it from historical data. In the current study, J.L.Mattson was listed as the study director, P.J.Spencer, was listed as study monitor, FOB observer. While R.R.Albee, was not listed as a participent in the current study.

Appendix E: Neuropathology proficiency report
In this report, 3 groups of rats (n=5/each) were treated with either: a single dose (by oral gavage) of 7 mg/kg of trimethyltin (TMT) in water on day 1, repeated oral gavage with 35 mg/kg/day of acrylamide 5 times/week for 3 weeks, or distilled water by gavage 5 times/week for 3 weeks. Neuropathological lesions consistent with neurotoxicosis of both chemicals were detected.
1. There was no laboratory identification (lab report number) for this proficiency report, which makes it difficult to be traced back.
2. The above mentioned study was not executed at the same time as the current study (MRID # 44192601). This neurohistopathological study was dated 06/25/93, while the current study was dated 07/09/1996.
3. The above study was conducted with two different chemicals, and two different dosaging procedures.
4. The author of the proficiency report concluded that "The methods, skills and judgement exercised by the study personnel were adequate to detect significant neurotoxic effects of these chemicals when administered to rats". However, several individuals, who conducted the above mentioned study, were not participant in the current study (MRID # 44192601). The proficiency report was authored by J.F.Quest, however; the light microscopist on the study was listed as Barry Yano. J.F.Quest was listed as the veterinary pathologist on the current study (MRID # 44192601). Perfusion and ganglia dissection was conducted by Debra Winieckie and LeeAnn Pugh, while in the current study, it was conducted by T.G.Sanderson. The role of J.F.Quest in the positive control pathology study needs to be clarified.

Generally, positive control data were submitted as three separate appendices, with different test chemicals, procedures, and dosage regiments. The opinion of the EPA reviewer is that the three studies were incompatible with the current study (MRID #

44192601). With that in mind, in addition to lack of neurotoxicity at the highest dose of XDE-564 utilized (2000 mg/kg), and insufficient neurotoxicology reports in the scientific literature addressing XDE-564 potential neurotoxicity, it becomes extremely difficult to judge the data from the current study, without adequate and well designed positive control data set. Positive control data should be reported from studies, as similar as possible, to the current study, regarding experimental design, treatment regimens, route of administration of the test compound, personnel conducting the study, etc.

6. Statistics - Statistical analyses were conducted on body weights, grip performance, rectal temperatures, landing foot splay, and motor activity. The average of three grip performance trials, and the average of three landing foot splay values, were used for statistical analyses. Motor activity counts were reported as their square roots to minimize problems of heterogeneity of variance and departure from normality that commonly occur from treatment. Means and standard deviations were calculated and homogeneity of variance was confirmed with the F-max test (alpha = 0.01). Factorial repeated-measures analysis of variance (ANOVAs) was used for initial statistical analysis. Tabulated values were reported as means ± SD.

C. METHODS:

1. Observations:
Animals were inspected twice daily for signs of toxicity and mortality. Clinical observations were conducted once a day (hand-held animals) on test days 2, 3, and 4.

2. Body weight:
Animals were weighed on days -7, 1, 2, 8, and 15 relative to the day of dosing (day 1).

3. Food consumption and compound intake: N/A

4. Ophthalmoscopic examination: Not conducted, however, external examination of the eyes was conducted as part of periodical clinical examination.

5. Cholinesterase Determination: Not conducted.

6. Clinical, Behavioral and Neurotoxicological Assessments:

A. Cageside and Clinical (hand-held)Observations: A visual evaluation for morbidity, moribundity, and mortality, the availability of feed and water, and treatment-related effects was conducted twice a day. These observations included evaluation of the skin, fur, mucous membranes, respiration, central nervous system function (including tremors, convulsions and bowel movement), and animal behavior. Clinical observations are comparable to the hand-held portion of the FOB. Clinical

observations were conducted once a day on test days 2, 3 and 4. These included hand-held observations of general appearance (thin, fat, red ocular/nasal crusts, etc.), palpebral closure, lacrimation (clear periocular wetness), salivation (clear perioral wetness), abnormalities of skin or haircoat, perineal staining, abnormal movements (e.g. muscle tone, tremors, convulsions), abnormal respiration (e.g. increased wheezing), reactivity to handling. Positive observations were entered directly into a computer as stated in MRID # 44192601.

B. Functional Observational Battery (FOB):
The FOB was conducted after motor activity testing on 10 animals/sex/dose group, prior to dosing (pre-exposure), on the day of dosing (day 1) approximately 5 hours after administration of the test material, and on days 8 & 15 of the study period. The rats were fasted the night before each FOB. The observer was blinded to the treatment status of the animals. The FOB included: a) hand-held and open-field observations, b) measurements of grip performance, c) landing foot splay, and, d) rectal temperature.

a) Hand-held and open-Field Observations:
Hand-held and open-field observations pre-exposure and on test day 1,8 and 15 included a careful physical examination and sensory evaluation according to an established format (Text Table II-1, page 20, MRID # 44192601).
Hand-held observations included general body status, palpepral closure, pupil size and reactivity, lacrimation, salivation, skin abnormalities, perineal staining, muscle tone, extensor-thrust response, abnormal movements and respiration, reactivity to handling, and resistance to removal from cage.
Open-field observations included activity, responsiveness to touch, sharp noise, and tail pinch, abnormal behavior, gait evaluation, quantitative evaluation of urine and fecal pellets voided during FOB.

b) Grip Performance:
Hindlimb grip performance was tested according to a standard procedure. Briefly, the rats were selected in a random manner. The observer then placed the rat's forelegs on a bench and the hindfeet were set on a horizontal screen attached to a strain gauge. The observer then smoothly but firmly pulled backward on the tail until the rat's grip on the screen was broken. The electronic strain gauge, linked to a personal computer (PC), recorded the rat's resistance to the pull in grams. The average of three trials was used for statistical analysis. Forelimb grip performance was similarly tested. In this application, a bench was not used, and the rats were placed so that the forefeet were on the screen and the hindfeet were on a smooth horizontal plastic surface. The test sequence was the same as for hindlimb testing (p.19, MRID # 44192601).

c) Landing foot splay:
The tarsal joint pad of each hindfoot was marked with ink. The animal was then dropped from a height of approximately 30 cm onto the recording sheet. This was repeated three times, and the tarsal pads were re-inked, if necessary, after the first and second drops. The distance from center-to-center of the ink marks was measured (cm) and the average of the three splay values was used for statistical analysis.

d) Rectal temperature:
Rectal temperature (^{0}C) was measured for all rats at pre-dosing, days 1,8, and 15 of the study.

C. Measurement of Motor Activity:
Motor activity system: Twenty-four motor activity cages (chambers), visually isolated from each other, were located in a quiet, dimly-lit room. Each motor activity cage consisted of a clear plastic circular alley equipped with an infrared photobeam that bisected the cage so that the beam crossed the alley in 2 locations. Each animal was tested individually for motor activity before the FOB, with each beam break that lasted > 100 msec was counted as an activity. All test sessions consisted of six 8-minute epochs, totaling 48 minutes of testing/animal. Animals were fasted overnight prior to each evaluation. Motor activity was monitored by a computerized system. Testing chambers were calibrated daily prior to testing. Calibration was performed with a rod (attached to a rotary motor) that broke the infrared beam (p. 27-29, MRID # 44192601).

7. Sacrifice and Pathology
Necropsy: All animals were sacrificed on schedule. Following 16 days, 5 randomly selected fasted rats/sex/dose were heparinized approximately 10 minutes prior to perfusion, and were anesthetized by methoxyflurane inhalation. Rats were perfused intracardially with 0.05 M phosphate buffer containing 0.7% sodium nitrite, followed by a phosphate-buffered solution of 1.5% glutaraldehyde-4% formaldehyde (c.540 mOsM). A complete gross examination of tissues was conducted on all animals by the study pathologist. The remaining 5 rats/sex/dose were fasted overnight, anesthetized by methoxyflurane inhalation and decapitated, but were not perfused-fixed. They were necropsied in a similar manner as indicated above. Tissues from these rats were fixed by immersion in neutral, phosphate-buffered 10% formalin.
Tissues collection and preservation: The following tissues were collected at necropsy for histopathological evaluation: ADRENAL GLANDS, MESENTRIC TISSUES, AORTA, NASAL TISSUES, AUDITORY SEBACEOUS GIANDS, ORAL TISSUES, BONE (INCLUDING JOINT), OVARIES, BONE MARROW, OVIDUCTS, BRAIN, PANCREAS, CECUM, PARATHYROID GLANDS, CERVIX, PERIPHERAL NERVES, COAGULATING GLANDS, PITUITARY GLAND, COLON, PROSTATE, DUODENUM, RECTUM, EPIDYMDES, SALIVARY GLANDS, ESOPHAGUS, SEMINAL VESCLES, EYES, SKELETAL MUSCLE, GROSS LESIONS, SKIN AND SUBCUTIS, HEART, SPINAL CORD (CERVICAL, THORACIC, LUMBAR),

ILEMEUM, JEJUNUM, SPLEEN, KIDNEYS, STOMACH, LACRIMAL/HARDERIAN GIANDS, TESTES, LARYNX, THYMUS, LIVER, THYROID GLAND, LUNGS, TONGUE, MAMMARY GLAND, TRACHEA, MEDIASTINAL LYMPH NODE, URINARY BLADDER, MEDIASTINAL TISSUES, UTERUS, MESENTRIC LYMPHNODE, VAGINA.

Tissues for neuropathologic evaluation, were prepared from all perfusion-fixed rats in the control and high-dose groups. Nine transverse sections of the brain were prepared from the: olfactory lobe, cerebrum (frontal, parietal, temporal and occipital lobes), thalamus/hypothalamus, midbrain, pons, cerebellum, and medulla oblongata. The following tissues were also prepared: trigeminal ganglia and nerve, pituitary gland, eyes with optic nerves, spinal cord (cervical and lumbar), nasal tissues with the olfactory epithelium and skeletal muscles (gastrocnemius and anterior tibial muscles). Tissues from the central nervous system and sections of skeletal muscle were embedded in paraffin, sectioned approximately 6 um thick, and stained with hematoxylin and eosin (H&E). Peripheral nerves (sciatic, tibial and sural) and dorsal root ganglia with roots (cervical and lumbar) were osmicated, embedded in plastic, sectioned approximately 2 um thick, and stained with toluidine blue. All tissues were examined by the study pathologist using a light microscope (P. 31-35, MRID # 44192601)

II. **RESULTS**

A. Observations :

1. Toxicity - No signs or symptoms, indicative of neurotoxicity, were observed in this study.

2. Mortality - None of the animals died, or had to be sacrificed during the course of this study.

B. Body weight and weight gain: No treatment-related effects were seen in body weights at any time during the study . Table 2 shows the results of the data analysis.

Table 2. MEAN BODY WEIGHTS (g) FOR RATS ADMINISTERED XDE-564 BY ORAL GAVAGE[ab].

Group	Sex	1	2	3	4
Dose/day		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg
Predosing	M	210±10	209±8	207±8	212±7
	F	147±5	145±4	143±5	144±4
Day 1	M	219±11	217±9	216±12	222±7
	F	148±4	147±5	145±4	146±4
Day 8	M	226±14	223±9	222±13	230±7
	F	151±6	149±7	148±6	148±5
Day 15	M	237±16	230±11	231±16	239±9
	F	155±7	153±8	152±5	153±5

a Data extracted from Table 12, page 72, MRID # 44192601
b n=10 for all groups and time points

C. Cageside and Clinical Observations: No treatment-related significant effects were observed at any time during the study. Perineal soiling that was observed in a few rats may be attributed to the test material vehicle (methyl cellulose).

D. Functional Observational Battery (FOB): Treatment did not affect hand-held and open-field observations, hindlimb or forelimb grip performances (Tables 3 & 4), landing foot splay (Table 5), or rectal temperature (Table 6) at any dose.

Table 3. MEAN HINDLIMB GRIP PERFORMANCE (g FORCE) OF RATS ADMINISTERED XDE-564 BY ORAL GAVAGE[ab].

Group	Sex	1	2	3	4
Dose/day		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg
Predosing	M	321±42	316±62	295±62	289±65
	F	217±49	203±31	197±29	205±36
Day 1	M	322±59	344±76	348±54	318±34
	F	246±64	228±31	225±38	235±43
Day 8	M	339±76	338±93	338±69	347±71
	F	214±38	210±49	230±43	222±42
Day 15	M	316±47	379±90	320±55	356±71
	F	203±54	207±40	222±33	217±30

a Data extracted from Table 14, page 74, MRID # 44192601
b n=10 for all groups and time points

Table 4. MEAN FORELIMB GRIP PERFORMANCE (g FORCE) OF RATS ADMINISTERED XDE-564 BY ORAL GAVAGE[a].

Group	Sex	1	2	3	4
Dose/day		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg
Predosing	M	300±69	293±118	288±39	306±92
	F	279±96	260±96	246±41	236±59
Day 1[b]	M	349±64	323±127	365±82	347±75
	F	310±80	282±77	252±58	279±68
Day 8	M	331±105	327±132	335±94	304±79
	F	282±87	237±64	279±39	293±58
Day 15	M	364±106	322±123	306±68	336±84
	F	241±100	221±32	229±52	229±57

a Data extracted from Table 16, page 76, MRID # 44192601
b n=10 for all groups and time points

Table 5. LANDING FOOT SPLAY (cm) OF RATS ADMINISTERED XDE-564 BY ORAL GAVAGE[a].

Group	Sex	1	2	3	4
Dose/day		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg
Predosing	M	5.9±0.9	6.0±0.8	5.3±0.8	5.7±0.6
	F	5.0±0.9	4.9±0.7	4.9±0.6	4.5±0.7
Day 1[b]	M	6.2±0.7	5.9±0.8	5.7±0.5	5.9±0.7
	F	5.2±0.8	5.2±0.9	4.8±0.5	4.8±0.5
Day 8	M	6.0±0.5	5.8±0.7	5.7±0.6	5.7±0.9
	F	4.8±0.8	5.1±0.7	4.7±0.8	4.5±0.7
Day 15	M	6.4±0.6	6.1±0.7	5.9±0.5	6.1±0.5
	F	5.0±0.5	5.2±0.4	4.8±0.6	4.8±0.4

a Data extracted from Table 18, page 78, MRID # 44192601
b n=10 for all groups and time points

Table 6. MEAN RECTAL TEMPERATURE (^{0}C) OF RATS ADMINISTERED XDE-564 BY ORAL GAVAGE[a].

Group	Sex	1	2	3	4
Dose/day		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg
Predosing	M	38±0.9	37.8±0.7	38±0.7	37.7±0.9
	F	37.3±0.7	37.3±0.8	37.6±0.6	37.4±0.6
Day 1[b]	M	38.1±0.5	38.1±0.4	38.5±0.4	38±0.5
	F	37.4±0.6	37.5±0.5	37.5±0.5	37.5±0.4
Day 8	M	38±0.7	38±0.5	37.8±0.5	38.3±0.4
	F	37.8±0.5	37.7±0.4	37.9±0.5	37.6±0.5
Day 15	M	38±0.4	38.2±0.4	38.1±0.3	38±0.3
	F	37.7±0.4	37.8±0.4	37.8±0.5	38.1±0.6

a Data extracted from Table 20, page 80, MRID # 44192601
b n=10 for all groups and time points

E. Measurement of Motor Activity:

No treatment-related effects were seen in motor activity at any time during the study. Table 7 shows the mean values and the standard deviation of the square root for total motor activity counts for each sex by treatment groups. However, it was difficult to interpret the square roots data submitted by the author. EPA reviewers request that the original (untransformed) data be submitted by the registrant.

Table 7. MEAN TOTAL MOTOR ACTIVITY (SQUARE ROOT OF TOTAL BEAM BREAKS) OF RATS ADMINISTERED XDE-564 BY ORAL GAVAGE[a].

Group	Sex	1	2	3	4
Dose/day		0 mg/kg	200 mg/kg	1000 mg/kg	2000 mg/kg
Predosing	M	9.1±1.1	9.4±1.5	10.2±1	9.2±1.9
	F	9+0.9	9.2+1.7	10.4+1.5	9.4+1.2
Day 1[b]	M	8.7±1.8	8.8±1.7	9.8±2.2	9.4±1.9
	F	8.4±1.5	8.9±1.4	9±0.9	9.5±2.7
Day 8	M	10.2±1.6	10.1±1.8	11±2.1	10.7±2
	F	9.4±1.8	9±1.9	9.3±1.5	9.4±1.2
Day 15	M	9.4±1.6	10.5±1.3	10.3±2.3	10.8±2.2
	F	8.4±1.3	9±2.2	9.8±2.2	8.8±2.7

a Data extracted from Table 22, page 82, MRID # 44192601
b n=10 for all groups and time points

F. Ophthalmoscopic examination - Ophthalmic examination was within normal limits.

G. Sacrifice and Pathology:

1. Organ weight - Not conducted

2. Gross pathology - All rats survived the treatment period and were necropsised at the scheduled time. No significant gross pathological lesions were observed during necropsy to be interpreted as a result of treatment.

3. Microscopic pathology - There were no histopathological evidence of XDE-564-induced neurotoxicosis in this study. The few detected histopathological lesions in the nervous tissues were equally distributed in the control and high-dose groups, or were only detected in the control group (e.g. Multi-focal degeneration of individual nerve fibers in the trapezoid body, dorsal root ganglia, and the tibial nerve). These changes

consistent with those observed in Fischer 344 rats as spontaneously occurring.

III. DISCUSSION

A. The purpose of this study was to evaluate the potential acute neurotoxicity of XDE-564 following oral (gavage) administration. In this study (MRID # 44192601), rats (10/sex/group) received a single dose of XDE-564 (97.6% a.i.) by gavage (in methyl cellulose). Doses were 0, 200, 1000, or 2000 (a limit dose) mg/kg for both sexes. Clinical observations were recorded twice daily. Evaluation during the two-week study period included body weights, functional observational battery (FOB), motor activity and neuropathology. The FOB consisted of hand-held and open-field observations, grip performance, rectal temperature and landing foot splay testing. Animals were evaluated by FOB and motor activity assay once prior to exposure, on day 1 (beginning approxixnately 5 hours after dosing), and on days 8 and 15 of the study period. Body weights were determined on days -7,1,2,8 and 15 relative to the day of dosing (day 1). Cholinesterase inhibition was not evaluated.

At study termination on day 16, 5 rats/sex/group were perfused intracardially with glutaraldehyde/paraformaldhyde, and histopathological evaluation of peripheral and central nervous system tissue was performed.

No evidence of neurotoxicological effects were observed at any of the dose levels. Furthermore,there were no compound-related effects in mortality, morbidity, clinical signs, body weight, FOB, motor activity or neuropathology.

Additionally, a gavage range-finding study (MRID # 44103522) was conducted to determine the benchmark dose (3 rats/sex). This dose-ranging study is acceptable.

A positive control data were submitted as three separate appendices, with different test chemicals, procedures, and dosage regiments. The opinion of the EPA reviewer is that the three studies were incompatable with the current study (MRID # 44192601). Consequently, the positive control data are rejected.

The LOAEL is not observed, based on lack of toxicity at any of the dose levels. The tentative NOAEL is 2000 mg/kg for both sexes, pending submission of requested information.

This acute neurotoxicity study is classified **Unacceptable/Guideline** pending submission of untransformed motor activity data and sufficient positive control data to satisfy EPA reviewers. This study does not satisfy the guideline requirement for an acute neurotoxicity study (81-8) in rats.

B. Study deficiencies:

The major deficiency of the current study is positive control data, which were submitted as three separate appendices, with different test chemicals, procedures, and dosage regiments.

These three studies appeared to be incompatible with the current study (MRID # 44192601). With that in mind, in addition to lack of neurotoxicity at the highest dose of XDE-564 utilized (2000 mg/kg), and insufficient neurotoxicology reports in the scientific literature addressing XDE-564 potential neurotoxicity, it became extremely difficult to judge the data from the current study, without adequate and well designed positive control data set.

Positive control data should be reported from studies, as similar as possible, to the current study, regarding experimental design, treatment regimens, route of administration of the test compound, personnel conducting the study, etc.

The registrant also needs to submit the untransformed data for the motor activity portion of the study, instead of the square roots data currently available for EPA reviewers.